Patent Application

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【Applicant】

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【Designated Patent Attorney】 Origin line.

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【Title of Invention】 The HPV-16 L1 VLP and HPV-18 L1 VLP vaccine.

【English Title of Invention】 HPV-16 AND -18 L1 VLP VACCINE

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【Claim of Priority】

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【Purport】

We respectfully submit an application stating the above with the Commissioner of the Korean Intellectual Property Office.

Agent patent corporation Nam AenD south (the signature or the phosphorus)

【Official Fee】

【Application Fee】	0 page(s) 38,000 won.
【Additional Application Fee】	31 page 0 won.
【Priority Fee】	36,000 2 cases the won.
【Examination Fee】	0 claim 0 won.
【Total】	74,000 won.

Description of the Invention

【Title of Invention】

The HPV-16 L1VLP and HPV-18 L1VLP vaccine [HPV-16 AND -18 L1 VLP VACCINE].

【Technical Field】

【0001】It relates to provide the protection about the infection in which the invention is caused by the VLP from the human papilloma virus (HPV) and its medical use, especially, the different kind HPV type and/or the disease.

【Background Technique】

【0002】Very the papilloma virus is the species-specific small DNA tumor virus. So far, at least 100 each human papilloma virus (HPV) genotypes are written. HPV is specific for the generally about skin (for example, the HPV-1 and -2) or mucosal surface (for example, the HPV-6 and -11) and the benign tumour (vegetation) usually continued for for several months or the number year is caused. It has to the individual in which such benign tumour relates and it can be distressing. But life is not threatened excluding the some exception.

【0003】The related has the some HPV known as the oncogenicity HPV type with moreover, the cancer. It is the correlation in which the positive correlation between the human cancer and HPV which is most powerful exist between the HPV-16, the HPV-18 and uterine cervix cancer kind (cervical carcinoma). Every year the uterine cancer is the malignant tumor which is commonest in the developing country in which the new patient of about 500,000 people is generated in world.

【0004】The other HPV drawing attention in connection with the cancer is the type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

【0005】The HPV virus analogous particle (VLP) had been being proposed to the potential vaccine for the treatment of HPV. (reference as to the study of animals, VLP shows about the infection of the other HPV type nots producing the cross protection: the Suzich, J A, the et al, and the Proc Natl Acad Sci.92: 11553-11557, 1995 and breitburd, seminars in Cancer Biology, vol 9, 1999, pp 431-445).

【0006】The vaccine protected about multiple HPV types is still needed.

【0007】The invention tries to handle such necessity.

【Content of Invention】

【0008】In the first form. And the invention relates to the use of the mixture comprising the HPV 16 VLP as to the prevention of the infection caused by at least one of the group of the oncogenicity HPV type except for the type 16 and 18 or the disease and HPV 18 VLP.

【0009】The invention relates to the use of the mixture comprising the HPV 16 VLP as to the manufacture of the medicine for the prevention of the infection caused by at least one of moreover, the group of the oncogenicity HPV type except for the type 16 and 18 or the disease and HPV 18 VLP.

【0010】In the second form. And the invention relates to the HPV type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, the HPV 16 VLP as to the prevention of the infection caused by at least one of the group of 68 or the disease, and the use of the mixture including the HPV 18 VLP.

【0011】The invention relates to moreover, the HPV type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, the HPV 16 VLP as to the manufacture of the medicine for the prevention of the infection caused by at least one of the group of 68 or the disease, and the use of the mixture of the HPV 18 VLP.

【0012】In the third form. And the invention relates to the HPV type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and the use of the HPV 16 VLP as to the prevention of the infection caused by at least one of the group of 68 or the disease.

【0013】The invention relates to moreover, the HPV type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and the use of the HPV 16 VLP as to the manufacture of the medicine for the prevention of the infection caused by at least one of the group of 68 or the disease.

【0014】In four the form. And the invention relates to the HPV type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and the use of the HPV 18 VLP as to the prevention of the infection caused by at least one of the group of 68 or the disease.

【0015】The invention relates to moreover, the HPV type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and the use of the HPV 18 VLP as to the manufacture of the medicine for the prevention of the infection caused by at least one of the group of 68 or the disease.

【0016】More, especially. And the invention relates to the method for inducing the immune reaction about at least one HPV type selected from the group which administers the composition to the subject is formed of all oncogenicity cancer types except for the type 16 and 18 comprising the HPV 16 VLP. The method in which the HPV type is selected from the group consisting of the type 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 is the be desirable. The method for inducing the immune reaction among the HPV type selected from the group consisting of the HPV 31, the HPV 33, the HPV 35, the HPV 52 and HPV 58 about one or greater is moreover, the be desirable. The method for inducing the immune reaction among the HPV type selected from the group consisting of the HPV 31, and the HPV 35 and HPV 58 about one or greater is most, the be desirable. In another embodiment, the composition which is useful in such method further comprises the HPV 18 VLP and/or the adjuvant. In yet another embodiment, the prevention of the infection by the HPV type in which the induced immune reaction is enumerated is caused.

【0017】In the additional embodiment. And the invention relates to the method for inducing the immune reaction about at least one HPV type selected from the group which administers the composition to the subject is formed of all oncogenicity cancer types except for the type 16 and 18 comprising the HPV 18 VLP. The composition including the HPV 18 VLP is administered to the subject the method for inducing the immune reaction among the HPV type selected from the group formed with 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 of 68 about one or greater is the be desirable. The method for inducing the immune reaction among the HPV type selected from the group consisting of the HPV 45 and HPV 58 about one or greater is the be desirable. In another embodiment, the composition which is useful in such method further comprises the HPV 16 VLP and/or the adjuvant. In yet another embodiment, the prevention of the infection by the HPV type in which the induced immune reaction is enumerated is caused.

【0018】* The above-mentioned described method for inducing (it is suitable for the size of the group doing with desirable) immune reaction among the confirmed specific group about the arbitrary 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 HPV type is the be desirable.

【Detailed Description for the Implementation of the Invention】

【0019】In the present invention, the cross protection the providing was surprisingly found out among the group of oncogenicity HPV type (the type 16 and 18 exclusion) which could cause the cancer if the inventors used the HPV 16 VLP and HPV 18 VLP about the infection by one or greater. The group of the oncogenicity type includes 66 with the type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82, 26, 53 or it is formed of this. Especially, if the HPV 16 VLP and HPV 18 VLP are used, the cross protection is provided concerning the infection and/or the disease caused by the group of the HPV type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 called the group of 'high-danger cancer type'. The protection about the combination of the protection about the entire group of the high-danger cancer type and specific type and type are confirmed. Moreover, it is except the protection effect that such effect shows up about the HPV 16 and HPV 18 'allogenic' by using the HPV 16 VLP and HPV 18 VLP. In this way, the HPV 16 VLP and HPV 18 VLP may be used in the HPV 16, and the vaccine about the HPV 18 and the other HPV type.

【0020】In the cross protection is the present application, it means than the group in which the attack rate of the infection (it is the persistent infection) about the group of the oncogenicity HPV type and/or the oncogenicity disease caused by the HPV infection does not vaccinate in the HPV 16 VLP and/or 18 VLP, and each group which preferably vaccinates to the type 16 and 18 being lower. In the present invention, the complete cross protection about the group of the type or the type is not necessary and it provides that the cross protection of the arbitrary level is good in fact. Preferably, the infection and/or the disease is less shown than the vaccinated group in which the group in which the level of the observed cross protection is vaccinated is equal with 5% and more preferably, or, the infection and/or the disease is hereinafter less even shown less than 10% less than 15% less than 20% less than 25% less than 30% less than 35% less than 40% less than 45% less than 50% less than 55% less than 60% less than 65% less than 70% less than 80% to 100% with 90%.

【0021】By detecting the presence of the specific nucleic acid about the various oncogenicity type the cross protection can be evaluated in the vaccination group and control group. For example, it can perform using the technology entered in the WO03014402 associated with the detection of the DNA type in which the detection uses the LiPA system of the non-specific amplification of the HPV DNA like as described and after in especially, the literature [Journal of Clinical Microbiology(1999), 37(8): 2508-2517] including WO 99/14377 and letter (Kleter) etc. and the reference cited to excitation and these literatures the whole contents is integrated with the present application as the reference. But the proper method like the type specific PCR using the specific primer against each concern HPV type can be applied for the detection of the HPV DNA of the insample. The proper primer is known to the person skilled in the art or the sequence of the oncogenicity HPV type is known and it can be easily formed.

【0022】Appropriately, preferably the seronegative is shown about the HPV infection or preferably the female showing the seronegative the cross protection is observed about the HPV 16 and 18 in the female teenager of the sexual activity previous with group of women.

【0023】Preferably, it collectively shows up as the group of the high-danger cancer type like the arbitrary 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 type or actual as any one of and the same type evaluated by the protection showing up in the vaccinated group comparing for the control group) is the oncogenicity type of the arbitrary one except 16 or 18, for example, the group of the high-danger cancer type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 or 68 about the high-danger cancer type everyone. Possible combinations of 2, 3, 4, 5, 6, 7, 8, 9, 10 of the high-danger cancer type and 11 are especially taken into consideration and the multiple various 'group's of the VLP type individually handled by the present application exists as itself and it compares with the placebo group and the level of the cross protection can be analyzed about these. It is the be desirable to use the HPV 16 VLP and/or the HPV 18 VLP the prevention of the HPV infection by such group of the HPV type is provided.

【0024】Suitably, the present invention is to provide the cross protection about the infection by the group doing with the desirable of the following HPV type and/or the disease :

【0025】A. The group which comprises the HPV type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and one or greater among 68

【0026】B. The group of A which comprises the type 31 and type 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and one or greater among 68

【0027】C. The group of A or B which comprises the type 33 and type 35, 39, 45, 51, 52, 56, 58, 59, 66, and one or greater among 68

【0028】D. The group of A to C which comprises the type 35 and type 39, 45, 51, 52, 56, 58, 59, 66, and one or greater among 68

【0029】E. The group of A to D which comprises the type 39 and type 45, 51, 52, 56, 58, 59, 66, and one or greater among 68

【0030】F. The group of A to E which comprises the type 45 and type 51, 52, 56, 58, 59, 66, and one or greater among 68

【0031】G. The group of A to F which comprises the type 51 and type 52, 56, 58, 59, 66, and one or greater among 68

【0032】H. The group of A to G which comprises the type 52 and type 56, 58, 59, 66, and one or greater among 68

【0033】I. The group of A to H which comprises the type 56 and type 58, 59, 66, and one or greater among 68

【0034】J. The group of A to I which comprises the type 58 and type 59, 66, and one or greater among 68

【0035】K. The group of A including one or greater among the type 59 and type 66 and 68 to J.

【0036】L. The group of A including one or greater among the type 66 and type 68 to K.

【0037】Especially, that it was easy that it compared with the female letting vaccinate to the vaccine in which the inventors included the HPV 16 VLP and 18 VLP through the population and the placebo group was more infected with one or greater among the group of the high-danger cancer type it concluded. Therefore, the invention relates to the use of the composition comprising especially, the HPV 16 VLP as to the prevention of the infection within the population by one or greater among the high-danger cancer type and HPV 18 VLP. Preferably, preferably, more preferably, it is more effective within the population by the group in which the composition is formed of the high-danger cancer type as to the prevention of the infection than the placebo over 20% or less or 20% over 25% or less or 25% over 30% or less or 30% ; and more preferably, it is suitably more effective as to the prevention of the infection over 34% or less or 34% as to the prevention of the infection over 38% or less or 38%.

【0038】Preferably, the invention relates to the HPV 31, 33, 35, 52, the HPV 16 VLP as to the manufacture of the medicine for the prevention of the infection by one or greater among 58, and the composition including the HPV 18 VLP.

【0039】That it was easy that it compared with the female letting vaccinate to the HPV 16 VLP and 18 VLP through the population and the inventors the placebo group was more infected with one or greater among the group of the HPV type 31, 33, 35, 52 and 58 with 43% it concluded. Therefore, the invention relates to especially, the HPV 31, 33, 35, 52, the HPV 16 VLP as to the prevention of the infection within the population by one or greater among 58, and the use of the composition including the HPV 18 VLP. Preferably, more preferably, more preferably, it is more effective within the population by the group in which the composition is formed of the HPV 31, 33, 35, 52 or 58 as to the prevention of the infection than the placebo over 10% or less or 10% over 15% or less or 15% over 20% or less or 20% and it is more effective with 25%, 30%, 37% or it is appropriately more effective as to the prevention of the infection over 43% or less or 43%.

【0040】Preferably, the invention relates to the HPV 31, 35, the HPV 16 VLP as to the manufacture of the medicine for the prevention of the infection by one or greater among 58, and the composition including the HPV 18 VLP.

【0041】That it was easy that it compared with the female letting vaccinate to the HPV 16 VLP and HPV 18 VLP through the population and the inventors the placebo group was more infected with one or greater among the HPV type 31, and the group of 35 and 58 with 58% it concluded. Therefore, the invention relates to especially, the HPV 31, 35, the HPV 16 VLP as to the prevention of the infection within the population by one or greater among 58, and the use of the composition including the HPV 18 VLP. Preferably, preferably preferably it is more effective within the population by the group in which the composition is formed of the HPV 31, and 35 or 58 as to the prevention of the infection than the placebo over 15% or less or 15% over 20% or less or 20% over 25% or less or 25% and it is more effective less than 30% less than 35% less than 40% less than 45% less than 49% with 55% or less or the or greater and it is appropriately more effective as to the prevention of the infection over 58% or less or 58%.

【0042】Preferably, the invention relates to the composition comprising the HPV 16 VLP as to the manufacture of the medicine for the prevention of the infection by one or greater among the HPV 45 and 59 and HPV 18 VLP.

【0043】Especially, that it was easy that it compared with the female letting vaccinate to the vaccine in which the inventors included the HPV 16 VLP and 18 VLP through the population and the placebo group was more infected with one or greater among the group of the HPV type 45 and 59 it concluded. Therefore, the invention relates to the use of the composition comprising especially, the HPV 16 VLP as to the prevention of the infection within the population by one or greater among the HPV 45 and HPV 59 and 18 VLP. Preferably, preferably, more preferably, it is hereinafter more effective within the population by the group in which the composition has the HPV 45 and HPV 59 as to the prevention of the infection than the placebo over 20% or less or 20% over 25% or less or 25% with 30% ; and more preferably, it is more effective as to the prevention of the infection over 33% or less or 33%.

【0044】 Preferably, the present invention relates to the preventive approach of the HPV infection within the population, and here the HPV 16 VLP , and the vaccination by the HPV 18 VLP or their mixture provide the cross protection concerning the infection by the group of the HPV type which is all oncogenicity HPV type (the type 16 and 18 exclusion), and the group of the group: HPV 45 of the group: the HPV 31, 33, 35, 52, 58 of the short circuit A described in the above to any one of group prescribed in L, the high-danger cancer type group, the HPV 31, 35, 58 and 59 and the protection obtained about all members of the group is higher than the protection which collectively shows up in the placebo.

【0045】 Preferably, the composition including the HPV 16 VLP and HPV 18 VLP provides the cross protection concerning one or greater among the HPV 35 and HPV 52 infection.

【0046】 Preferably, preferably the composition of the HPV 18 VLP and HPV 16 VLP provides the protection about the infection by the HPV 16 and the HPV 18 both with moreover, the HPV 18 and/or the HPV 16.

【0047】 The invention relates to moreover, one among the group of the high-danger cancer type, preferably, the HPV 31, 33, 35, 52, the group or 31 consisting of 58, and 35, and the use of the HPV 16 VLP as to the prevention of the infection by the group consisting of 58.

【0048】 The invention relates to moreover, one among the group of the high-danger cancer type, preferably, the HPV 31, 33, 35, 52, the group or the HPV type 31 consisting of 58, and 35, and the use of the HPV 16 VLP as to the manufacture of the medicine for the prevention of the infection by the group consisting of 58.

【0049】The invention also relates the use of the HPV 18 VLP as to the prevention of the infection by the group which preferably is formed among the group of the high-danger cancer type over one with the HPV 45 of 59.

【0050】The HPV 16 VLP of the invention can be used under the member of the dissimilar HPV VLP type or the member can be used with another HPV VLP type. Preferably, the HPV 16 VLP is used with the HPV 18 VLP.

【0051】The HPV 18 VLP of the invention can be used under the member of the dissimilar HPV VLP type or the member can be used with another HPV VLP type. Preferably, the HPV 18 VLP is used with the HPV 16 VLP.

【0052】Preferably, preferably the HPV 16 VLP , and the HPV 18 VLP and their mixture are used in order to provide the high-danger cancer type, especially, the protection about the HPV type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68.

【0053】* The cross protection effect, preferably, the immunogenic composition of the invention, more preferably, the HPV 16 VLP and HPV 18 VLP mixture may be used in the active immunity (active immunization) of the female teenager in which the adult female and age are 10 years old in order to prevent one or greater among the HPV-16 and HPV-18 infection, and the persistence HPV-16, the HPV-18 infection, the HPV-16 and HPV-18 related uterine cervix cancer.

【0054】Preferably, it is used so that the immunogenic composition of the invention prevent the endocervical neoplasia associated with the infection by the dissimilar (except the HPV 16, and 18) oncogenicity type.

【0055】As the widely the method for the production of the HPV VLP and VLP are known in the relevant field. Generally VLP is arbitrarily formed with the L1 of the virus from the L2 structural protein quality (reference: the WO9420137 and WO9405792). In the present invention, the proper HPV VLP such as the L1 and L1 + L2 VLP can be used it provides the cross protection.

【0056】Preferably, VLP is the L1 singleness VLP.

【0057】VLP may include the electrical field L1 protein.

【0058】Preferably, it is the L1 protein in which the L1 protein which is used it forms VLP is truncated (truncated). Preferably, the truncation removes the nuclear localization signal. Preferably, the truncation is C end truncation. Preferably, more preferably, C end truncation removes the amino acid less than 40 with the amino acid less than 50. In case VLP is the HPV 16 VLP preferably C end truncation removes the amino acid of 34 from the HPV 16 L1. In case VLP is the HPV 18 VLP preferably C end truncation removes the amino acid of 35 from the HPV 18 L1.

【0059】The appropriately the truncated L1 protein is the functionality L1 protein derivative. The functionality L1 protein derivative can cause the immune reaction (it is appropriately adjuvant added the when necessary) and VLP in which the immune reaction consists of the HPV type in which the electrical field L1 protein and/or the L1 protein originates can be recognized.

【0060】Functional dissimilar protein derivative in which the VLP of the invention includes moreover, deletion, and the mutant of the electrical field like the substitution or the insertional mutation or the truncated HPV L1 protein of the type is include might. The sequence where the proper derivative moreover ***s is included. The L1 protein or the derivative can be moreover, the fusion protein like the fused body of the L1 and L2 or the early protein. The L1 protein or functional protein derivative can form VLP and the VLP formation can be evaluated by for example, the standard technology like the electron microscope and dynamic laser light scattering.

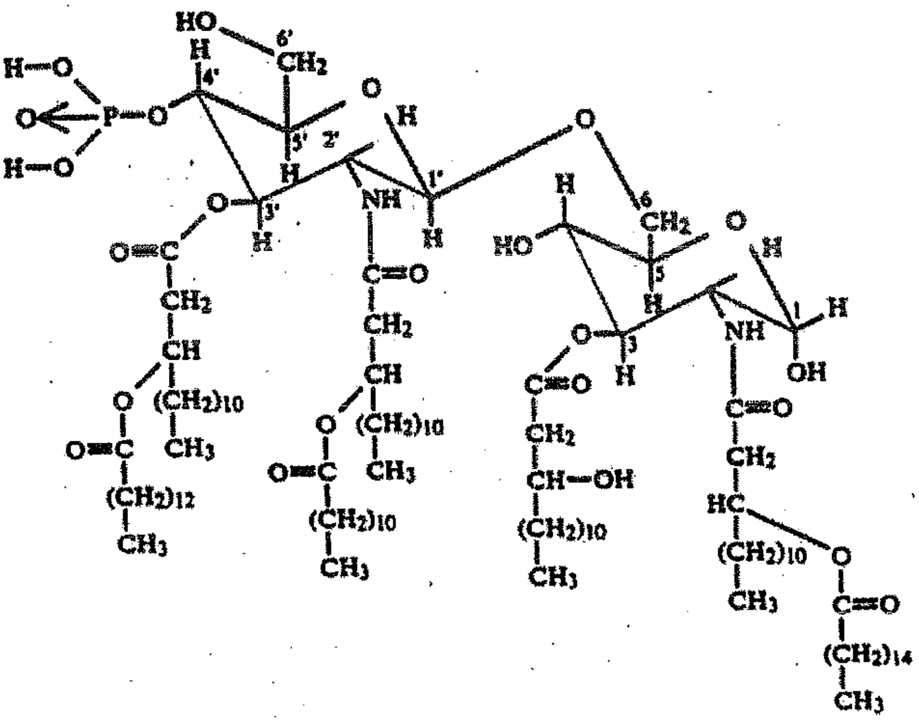
【0061】VLP can be made in the yeast cell or the insect cell, for example, the proper cell matrix like the baculovirus cell and as the widely the technology for the manufacture of VLP is known in the relevant field and it is entered in the WO9913056, in which the whole contents is integrated with for example, the present application as the reference the US6245568 and the reference cited to excitation.

【0062】Preferably VLP is manufactured by decomposition and reassembly technology and this can be more stable and the papilloma virus VLP uniform can be provided. For example, in literatures [McCarthy et al, 1998 "Quantitative Disassembly and Reassembly of Human Papillomavirus Type 11 Viruslike Particles in Vitro" J. Virology 72(1):33-41]s, what in order to obtain the uniform product of VLP, the recombining L1 HPV 11 VLP refined from the insect cell is disassembled and reassembles is written. In the WO9913056 and US6245568, the method for reassembling the decomposition / for manufacturing the HPV VLP is moreover written.

【0063】Preferably, every the HPV VLP of the invention is manufactured for the WO9913056 or the US6245568 like as described.

【0064】The VLP of the invention can be mixed with the adjuvant. The vaccine of the invention comprises the other reagent stimulating the non-toxic derivative of the lipid A which becomes avirulent from the arbitrary source and lipid A, and saponin and TH1 type reaction. And the adjuvant or the proper immunostimulant which is not limited is include might thus.

【0065】The what is called stimulant in which it has the lipopolysaccharide (LPS) of the enterobacteria with the effect of the immune system was from long time ago known. But it had been being therefore omitted with its toxic effect to use this as the adjuvant. The monophosphoryl lipid A (MPL) which is the non-toxic derivative of LPS which is generated by removing the core carbohydrate and phosphate from the reducing end glucosamine is written in literature (1986, Immunology and Immunopharmacology of bacterial endotoxins, Plenum Publ. Corp., NY, p407-419) including the Ribi etc. and the following structure is carried :



【0066】

【0067】Another variant which becomes avirulent of MPL removes from 3-position of the disaccharide backbone of the acyl chain and 3- position is generated and this is called as 3-O- acylation monophosphoryl lipid A (3D-MPL). It can be refined with the method in which this is taught in GB 2122204B and it be manufactured and moreover, the formulation method of its 3-O-acylation variant and diphospho reel lipid A is written in literature.

【0068】It is the form of the emulsion in which the form done with the desirable of 3D-MPL carries small particle size in which the diameter is less than 0.2 ㎛ and the form is known in the manufacturing method thereof silver WO 94/21292. The aqueous formulation including the monophosphoryl lipid A and surfactant is written in the WO9843670A2.

【0069】The adjuvant induced in the composition of the invention with the lipopolysaccharide of the bacteria to shape can be refined from the source of bacteria and it can be processed or alternatively it can be synthesized. For example, the Salmonella species (the refined monophosphoryl lipid A is written in literature [1986, and the see above] including the Ribi etcSalmonellasp.Induced 3-O- acylation monophosphoryl or the diphospho reel lipid A is written in GB 2220211 and US 4912094. The compounded refined with other lipopolysaccharide is the literature [Hilgers.etal., 1986, Int. Arch. Allergy. Immunol., 79(4): 392-6; Hilgers etal.It is written in the , 1987, the Immunology, and 60 (1) : 141-6: and EP 0 549 074 B1]. Especially, the bacterial lipopolysaccharide adjuvant done with desirable is 3D-MPL.

【0070】Therefore, in the present invention, the LPS derivative which can be used is LPS, MPL, or immunostimulants which are structurally similar to 3D-MPL. It can be the monosaccharide in which also, in other aspects, the LPS derivative is acylated of the invention and this is the sub - portion (sub-portion) toward the structure described in the above of MPL.

【0071】Saponin is taught in literature [Lacaille-Dubois, M and Wagner H. 1996. A review of the biological and pharmacological activities of saponins. Phytomedicine vol 2 pp 363-386]. It is the steroid or the triterpene glycoside in which the widely saponin is distributed in the plant and marine animal group. The colloidal solution is formed among the water in which saponin forms bubble in the shaking and with cholesterol is precipitated it is recorded. The case , and these of being in the cell membrane vicinity produce the pores (pore) analogous structures in the film and saponin causes the rupture of the film. For example, the hemolysis (haemolysis) of the red blood cell property or all saponins of the specific saponin are not so of such phenomenon.

【0072】Saponin is known as the adjuvant within the vaccine for the systemic medication. The adjuvant and hemolytic activity of each saponin are extensively studied in the relevant field (lacaille-Dubois and Wagner, and the see above). For example, the Quil A (it is induced from the rhytidome of the tree Quillaja saponaria Molina of the SouthAmerica) and its fraction is US 5,057,540 and literature ["Saponins as vaccine adjuvants", the Kensil, and the

C. RCrit RevTherDrugCarrierSystIt is written in the , 1996, and 12 (1-2) :1-55] and EP 0 362 279 B1.

【0073】The corpuscle construction of being called as the immunostimulating complex (ISCOMS) including the fraction of the Quil A had been being the haemolytic and it has been being used for the manufacture of the vaccine (Morein, B., EP 0 109 942 B1; WO 96/11711; WO 96/33739). The haemolytic saponin QS21 and QS 17 (the HPLC refinement fraction of the Quil A) are known as the general adjuvant having with effect and it as the manufacturing method thereof lice is known in US Patent No.5,057,540 and EP 0 362 279 B1. The other saponin which has been being used for the general vaccination research includes the saponin induced from the other ***, such as the Gypsophila elegans and Saponaria. And (Bomfordetal., Vaccine, 10(9):572-577, 1992).

【0074】The improved system comprises the none toxic lipid A derivative like being known in WO 94/00153, the mixture of the saponin derivative, especially, the QS21, and the reactogenic one composition which includes the mixture of 3D-MPL or in which the QS21 like being known in WO 96/33739 consists of cholesterol with the quenching (quenching).

【0075】The adjuvant formulation having with the effect includes the QS21 and 3D-MPL within the oil-in-water emulsion is written in WO 95/17210 and it is the formulation done with desirable.

【0076】Therefore, in one embodiment of the invention, the vaccine in which the non-toxic derivative of the detoxification lipid A or the lipid A is added to the adjuvant, and the vaccine in which more preferably, the monophosphoryl lipid A or its derivative is added to the adjuvant are provided.

【0077】Preferably, the vaccine includes additionally, saponin, and more preferably, the QS21.

【0078】Preferably, the additionally the formulation includes the oil-in-water emulsion. The invention also provides the method it mixes the L2 peptide of the invention with the pharmaceutically acceptable diluting agent like 3D-MPL for manufacturing the vaccine formulation.

【0079】The additional component which preferably exists within the vaccine formulation adjuvant added according to the present invention comprises the octoxynol like as described in the present application and the polyoxyethylene ester, especially, the bile salts like as described in the nonionic detergent like the T-octylphenoxypolyethoxyethanol (triton X-100) and polyoxyethylene sorbitan monooleate (tween 80) and present application or the cholic acid derivative, especially, the sodium deoxycholate or the tauro deoxycholate. Therefore, the formulation done with especially, the desirable comprises the L2 production of antigen water the proper vaccine is provided, 3D-MPL, which can be mixed the triton X-100, and the Tween 80, and the sodium deoxycholate.

【0080】The vaccine in the embodiment, done with one desirable of the present invention comprises cholesterol, saponin and the vesicularity adjuvant formulation including the LPS derivative. The adjuvant formulation done in connection with this with desirable includes cholesterol and the single thin film (unilamellar) parcel carrying the lipid bilayer including the phosphatidylcholine which is the dioleo the preferably is included and here saponin and LPS derivative are combined with the lipid bilayer or it becomes within the lipid bilayer with M bedding (embed). More preferably, here, these adjuvant formulations include 3D-MPL as saponin as the QS21 and LPS derivative QS21: more preferably, 1:1 to 1:100 weight / weight the ratio of cholesterol is 1:5 weight / weight. Such adjuvant formulation was written in EP 0 822 831 B and its statement content was integrated into the reference with the present application.

【0081】Appropriately, the vaccine of the invention is mixed with aluminum and aluminum is used and the appropriately is absorbed on the aluminum adjuvant or the partly is absorbed. Appropriately, preferably the aluminum salt the adjuvant is the mixture with 3D MPL like the aluminium phosphate and 3D MPL. The mixture with 3D MPL is moreover, arbitrarily the be desirable with aluminium hydroxide.

【0082】In the present invention, it is the mixture of the aluminum salt or the aluminum salt + 3D MPL and VLP it most does with desirable. The aluminium hydroxide is the be desirable as the aluminum salt.

【0083】The vaccine may include aluminum or the aluminum compound as moreover, the stabilizer.

【0084】The vaccine of the invention can be provided within the oral, local, subcutaneousness, the mucous membrane (generally, the intravaginal), within the vein through the intramuscular, the intranasal, the Sublingual, and the route like the intradermal or the various suppository.

【0085】Arbitrarily, the vaccine is formulated with the other HPV antigen such as the early antigen and non- HPV antigen or it can be comedicated. Appropriately, more preferably, these non- HPV antigens can provide the herpes simplex virus, EBV, and the protection about the venereal disease like the Chlamydia and HIV with etc disease. The inventors prefer that especially, the vaccine of the invention includes the gD from HSV or its truncate. In this way, the vaccine provides the protection for the HSV both and HPV.

【0086】The capacity of the component of vaccine will be various according to the state of the entity, sex, the age and weight, and the administration route and HPV of the vaccine. It can be changed according to the number of amount, moreover, the VLP types. Appropriately, the transmission carries amount of the vaccine which is suitable to generate the amynologic protective reaction. Appropriately, each vaccine content includes each VLP of 1 through 100μg, preferably, 5 through 80μg, more preferably, each VLP of 5 through 30μg, and more preferably, each VLP of 5 through 20μg and 5μg, 6μg, 10μg, 15μg or 20μg is especially, the be desirable.

【0087】Preferably the vaccine is the be desirable about all vaccines of the invention with 10 through 15 years old to be used for the vaccination of the female teenager of 10 through 13 years old. The seronegative can be shown about the HPV cancer type and or or the vaccine can be administered to the female who is the DNA voice following the aberrant Pap smear after the operation after the one of the lesion caused by HPV.

【0088】Preferably, the vaccine is delivered to 0, 1 month mode or 0, 1 and 6 month mode for example. Appropriately, the preferably the vaccine inoculation method includes the booster injection after 10 year after 5 through 10 year.

【0089】Preferably, the vaccine is the liquid vaccine formulation. However such vaccine is freeze-dried and it can be re-organized before the administration.

【0090】Preferably, in the present invention, the used immunogen (the HPV 16 VLP and/or the HPV 18 VLP) is used as the vaccine and it can be formulated using the proper diluting agent to the vaccine. Therefore, the present invention relates to especially, the use of the HPV 16 like the L1 singleness vaccine as to the prevention of the HPV infection or the HPV 18 vaccine.

【0091】* The invention is exemplified with reference to the embodiment unlimited the following.

【0092】**Embodiment.**

【0093】The healthy female between 15 through 25 years old was exempted to the mixture of the HPV 18 L1 VLP and HPV 16 L1 VLP. The registered female showed the seronegative about 1) HPV-16 and HPV-18 and it was the voice (the HPV PCR the detection) and the result partner less than 6 people was till now carried with 3) and 4) normal pap smear was shown about the high-danger HPV infection of 2) cervix.

【0094】The mixture included the HPV-16 L1 VLP of 20㎍ per 0.5㎖ capacity, and the HPV-18 L1 VLP of 20㎍ and the aluminium hydroxide of 500㎍ and 3D-MPL of 50㎍ were added to the adjuvant. The placebo group injected the aluminium hydroxide singleness of 500㎍.

【0095】The vaccine efficacy (V.E.) about the high-danger cancer HPV type was evaluated and it is improvement % compared with the placebo group in the protection about the infection by the vaccine which here is increased with V E.

【0096】By detecting the presence of the specific nucleic acid it evaluated as to the group and the control group in which the cross protection was vaccinated about the various oncogenicity type. It performed to the detection of the DNA type of after in which the detection used the non-specific amplification of the HPV DNA like as described and LiPA system in the WO03014402 and the reference cited to excitation in the technology like as described, especially, the literature [Journal of Clinical Microbiology(1999), 37(8):2508-2517] including WO 99/14377 and letter (Kleter) etc. and their whole contents was integrated with the present application as the reference.

【0097】But the proper method like the type specific PCR using the specific primer against each concern HPV type can be applied for the detection of the HPV DNA of the insample. The proper primer is known to the person skilled in the art or the sequence of the oncogenicity HPV type is known and it can be easily formed.

【0098】The vaccine efficacy evaluated about the high-danger cancer type whole of the twelve, and the infection for HPV-18 phylogenetic related type (45 and 59) and HPV-16 phylogenetic related types (31, and the group of the group : 31, 33, 35, 52 of 35 and 58 and 58).

【0099】The initial analysis is "ITT" (analysis object cohort (.Intention To TAll entities prescribed the reat cohort)), and the vaccine more than 1 time were shown it performed in the phase. This data showed in the table 1.

【0100】The corollary (in "ATP" (protocol for the patients in which the result showing for the table 2 and 3 agrees in all standards of the experiment.According To PIt is about the rotocol)) group. In the point of time when in the table 2, 18 month is over 50% of the cohort after their first vaccination, it is the center analysis of data obtained from all patients. The table 3 is the final result and all data originate in 18 month after the first vaccination (0 month) from the patient. In the ATP group, the vaccine was prescribed in 0, 1 and 6 month 3 times and all patients showed the seronegative in 6 month.

【0101】As shown in data written in the table 1 prove the immunity by the mixture of the HPV 16 VLP and HPV 18 VLP provide the obvious cross protection concerning the other HPV type. At this moment, the sample size was so small and the statistical analysis of being minute could not be provided. However data prove the tendency of the positivity and the immunity by the HPV 16 VLP and HPV 18 VLP suggests about the infection by the other HPV type being the effective thing.

【0102】It became positive as the research as to the this, proceeded.

【0103】It proves that the table 2 the HPV 16 and HPV 18 statistically provide the cross protection of the level of significance concerning the group of the high-danger cancer type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

【0104】The table 3 excludes the HPV-18 related type (the tendency to be very powerful is shown) and it proves that the cross protection of the level of significance statistically exists about the evaluated HPV 31, 35, and the group of the high-danger (it is not HPV-16) type of 58: HPV 31, 33, 35, 52, 58: and twelve.

【0105】

표 1

분석된 HPV 유형	감염된 여성의 수(백신 그룹)	감염된 여성의%(백신 그룹) = A	감염된 여성의 수(위약 그룹)	감염된 여성의%(위약 그룹) = B	백신 효능 % 1 – (A/B) x 100, 백신 및 위약 그룹의 상대 크기에 대해 조정됨	95% 신뢰 한계 - 하한	95% 신뢰 한계 - 상한	P
HPV 31,35, 58	5	1.1	11	2.4	55.1	-29.1	84.4	0.127
HPV 31, 33, 35, 52, 58	17	3.8	24	5.4	30.3	-29.7	62.6	0.252
HPV 45, 59	3	0.7	6	1.3	50.6	-97.7	87.6	0.309
HPV31,33,35, 39,45,51,52,56 ,58,59,66,68.	27	6.3	40	9.4	34.6	-6.5	59.9	0.086

샘플을 환자로부터 9, 12, 15 및 18개월째에 취하여, 상기의 특정된 유형에 의한 HPV 감염에 대해 테스트하였다.

【0106】

표 2. 부수적인 이종성 감염의 예방에 있어서 3차례의 투약후의 백신의 효능.

표 2 : HPV-16 계통발생적 관련 유형, HPV-18 계통발생적 관련 유형, HPV-16 및/또는 HPV-18 계통발생적 관련 유형 및 HPV-16 및 HPV-18을 제외한 모든 고위험성 유형에 의한 감염에 대한 백신의 효능 - ATP 코호트(6-18 개월)

감염 유형	발병률						백신 효능		
	백신			위약					
	N	n	AR	N	n	AR	%	95% CI	p-값
HPV-16 관련	433	12	2.8	438	24	5.5	49.4	0.2 74.4	0.060
HPV-16 관련*	423	29	6.9	423	46	10.9	37.0	1.6 59.6	0.052
HPV-18 관련	442	9	2.0	449	16	3.6	42.9	-27.9 74.5	0.223
HPV-16/18 관련	433	21	4.9	438	41	9.4	48.2	13.8 68.9	0.012
HPV-16/18 관련*	423	34	8.0	423	56	13.2	39.3	9.0 59.5	0.019
고-위험성**	385	53	13.8	386	88	22.8	39.6	17.7 55.7	0.001

N = 특정한 코호트내의 피검체의 수

n = 부수적 HPV 감염된 피검체의 수

AR = 발병률 = n/N

95% CI = 95% 신뢰 구간

하한 $= 1 - \exp(\log(arv / arp) + 1.96 * \mathrm{sqrt}(1/nv - 1/Nv + 1/np - 1/Np))$

상한 $= 1 - \exp(\log(arv / arp) - 1.96 * \mathrm{sqrt}(1/nv - 1/Nv + 1/np - 1/Np))$

백신에서의 발병자의 수가 0일 경우:

하한* $= 1 - \exp(\log(arv^{*} / arp^{*}) + 1.96 * \mathrm{sqrt}(1/(nv+0.5) - 1/(Nv+0.5) + 1/(np+0.5) - 1/(Np+0.5)))$

【0107】

상한* = 1- exp (log (arv* / arp*) – 1.96 * sqrt (1/(nv+0.5) – 1/(Nv+0.5) + 1/(np+0.5) – 1/(Np+0.5)))

arv = 백신 수여자에서의 발병률
arp = 위약 수여자에서의 발병률
nv = 백신 수여자에서의 발병자의 수
Nv = 백신 수여자에서의 발병자 및 비발병자의 수
np = 위약 수여자에서의 발병자의 수
Np = 위약 수여자에서의 발병자 및 비발병자의 수

HPV-16 관련: 기타 HPV 유형을 고려하지 않은 HPV-16 계통발생적 관련 유형 35, 31, 58
HPV-16 관련* : 기타 HPV 유형을 고려하지 않은 HPV-16 계통발생적 관련 유형 35, 31, 58, 33, 52
HPV-18 관련 : 기타 HPV 유형을 고려하지 않은 HPV-18 계통발생적 관련 유형 45, 59
HPV-16 및/또는 HPV-18 관련 : 기타 HPV 유형을 고려하지 않은 HPV-16 및/또는 HPV-18 계통발생적 관련 유형 35, 31, 58, 45, 59
HPV-16 및/또는 HPV-18 관련*: 기타 HPV 유형을 고려하지 않은 HPV-16 및/또는 HPV-18 계통발생적 관련 유형 35, 31, 58, 33, 52, 45, 59
** = HPV-16 및 HPV-18을 제외한 고-위험성 유형

【0108】

표 3

분석된 HPV 유형	그룹 당 이용가능한 정보를 지닌 피검체의 수의 전체수	감염된 여성의 수(백신 그룹)	감염된 여성%(백신 그룹) = A	감염된 여성의 수(위약 그룹)	감염된 여성%(위약 그룹) = B	백신 효능% 1 – (A/B) x 100, 백신 및 위약 그룹의 상대 크기에 대해 조정됨	95% 신뢰 한계 - 하한	95% 신뢰 한계 - 상한	P
HPV 31,35, 58	412	11	2.7	26	6.3	57.9	15.9	78.9	0.012
HPV 31, 33, 35, 52, 58	403	28	6.9	48	12.2	43.0	11.0	63.5	0.015
HPV 45, 59	421	10	2.4	15	3.6	33.5	-46.3	69.8	0.319
HPV31,33,35, 39,45,51,52,56 ,58,59,66,68.	368	58	15.8	90	25.3	37.7	16.2	53.6	0.002

샘플을 환자로부터 18개월째에 취하여, 상기의 특정된 유형에 의한 HPV 감염에 대해 테스트하였다.

Claims

【Claim 1】

The pharmaceutical composition in which the VLPs mixes the L1 protein or its immunological fragment of HPV with the adjuvant including the aluminum salt and 3-O- acylation monophosphoryl lipid A (3D-MPL) and included in the pharmaceutical composition which comprise the HPV type 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and the human papilloma virus (HPV) type 16 for the prevention of the infection caused by at least one oncogenicity HPV type selected from the group consisting of 68 and/or the disease and HPV type 18 virus analogous particle (VLPs).

【Claim 2】

As for claim 1
The pharmaceutical composition for the prevention of the infection caused by at least one oncogenicity HPV type selected from the group consisting of the HPV type 31, 33, 35, 52 and 58 and/or the disease.

【Claim 3】

As for claim 1
The pharmaceutical composition for the prevention of the infection caused by at least one oncogenicity HPV type selected from the group consisting of HPV type 31, and 35 and 58 and/or the disease.

【Claim 4】

As for claim 1
The pharmaceutical composition for the prevention of the infection caused by at least one oncogenicity HPV type selected from the group consisting of the HPV type 45 and 59 and/or the disease.

【Claim 5】

As for claim 1

The pharmaceutical composition for the prevention of the infection caused by the HPV type 31 and/or the disease.

【Claim 6】

As for claim 1

The pharmaceutical composition for the prevention of the infection caused by the HPV type 45 and/or the disease.

【Claim 7】

As for claim 1

The pharmaceutical composition for the prevention of the infection caused by the HPV type 52 and/or the disease.

【Claim 8】

As for claim 1

The pharmaceutical composition in which the extent of the prevention is excellent than the placebo over 15%.

【Claim 9】

As for claim 1

The pharmaceutical composition in which the adjuvant is the mixture of 3D MPL and aluminium hydroxide.

【Claim 10】

As for claim 1

The pharmaceutical composition in which the composition includes the HPV 16L1 VLPs of 20㎍ and HPV 18L1 VLPs of 20㎍ in the capacity of 0.5ml and the adjuvant includes the aluminium hydroxide of 500㎍ and 3D MPL of 50㎍.

【Claim 11】

The pharmaceutical composition in which the level of the prevention of the infection caused in the group of human by the group of the oncogenicity HPV type according to claim 1 and/or the infection showing up as the pharmaceutical composition including the HPV 16 for the prevention of the disease and HPV 18 VLPs in the group and/or the disease is lower than the group disposed as the placebo.

Abstract

【Summary】

The invention relates to the use of the HPV 18 VLP and HPV 16 VLP for providing the cross protection about the infection by the other HPV type and/or the disease.